UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

HED DOC. NO. 013504

DATE: **June 2, 1999**

MEMORANDUM

SUBJECT: ***CHLORPYRIFOS*** **- REPLACEMENT OF HUMAN STUDY USED IN RISK ASSESSMENTS -** Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland, Co-Chairman
And
Pauline Wagner, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Steve Knizner, Branch Senior Scientist
Re-Registration Branch 3
Health Effects Division (7509C)

PC Code: 059101

On February 2, 1999, the Health Effect Division's (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for chlorpyrifos and selected doses and toxicology endpoints for risk assessment, based solely on **animal toxicity studies**. The HIARC re-convened on February 23, 1999 to determine the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments. Presented in this report are the chronology of the various HIARC meetings on chlorpyrifos and a summary table of the doses and endpoints that are currently used for risk assessment of chlorpyrifos.

I. BACKGROUND

On **February 21, 1986**, the Health Effects Division's (HED) RfD/Peer Review Committee established the Reference Dose (RfD) of 0.003 mg/kg/day based on the NOAEL of 0.03 mg/kg/day in a study in humans and an Uncertainty Factor of 10 to account for intra-species variation. This RfD was re-affirmed at the subsequent meetings held on March 4, 1988, September 8, 1993, May 25, 1995 and November 23, 1995.

On **April 28, 1996**, HED's Toxicology Endpoint Selection Committee (TESC) selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments TES Document dated, August 15, 1994 **(HED Document No.** 013130).

On **December 11, 1997** , HED's Hazard Identification Assessment Review Committee (HIARC) re-assessed the RfD in response to a report (*Proposed Reference Dose (RfD) for Acute and Chronic Exposure to Chlorpyrifos Based on the Criteria Described by the Acute Cholinesterase Risk Assessment Task Force and the Available Animal and Human Data)* submitted by the Registrant (MRID No. 44271001). At this meeting, the HIARC also re-assessed the doses and endpoints selected for dietary and non-dietary exposure risk assessments by TESC, and discussed the critical scientific literature relevant to the potential risk to infants and children (as required by FQPA). The HIARC's conclusions are presented in the **HIARC report dated February 2, 1998 (HED Document No. 012471).**

On October 29, 1998 the HIARC evaluated the five additional studies listed below, the Registrant's rebuttal (of 8/4/98) and their impact on the RfD and FQPA assessment. Studies reviewed by HIARC were: Developmental Neurotoxicity (MRID No. 44556901 & 44661001); Cholinesterase and Metabolite Determination (MRID No. 44648102);Special Neurotoxic Esterase Assay (MRID No. 44273901); Cognitive Neurotoxicity (MRID No. 44020901) and Blood Time Course (Part A) (MRID No. 44648101). The HIARC's conclusions are presented in the **HIARC report dated December 7, 1998 (HED Document No. 013004).**

In **December 10-11, 1998**, the Science Advisory Board/Scientific Advisory Panel discussed both the ethical concerns and the scientific merit of using humans subjects for testing pesticides. The Agency is currently developing a policy for the use of human studies in risk assessment. In the interim, HED has taken the following course of action.

In **January, 1999**, the HIARC developed a specific outline of parameters and questions for the re-examination of human studies. Human studies were used in endpoint selection for risk assessment for eight organophosphates, including chlorpyrifos. These studies were re-evaluated according to the parameters and questions developed by the Committee. The HIARC then selected doses and endpoints from toxicity studies with animals for each of these eight organophosphate. The HIARC examined the human data in conjunction with the animal data to determine the appropriate inter-species uncertainty factor.

In the evaluation of the comparative toxicology data in laboratory animals and humans, when the data was suitable for comparison, the Committee relied mainly on the LOAEL for cholinesterase inhibition at comparable time points (duration). The comparative data was evaluated as follows:

> If the comparative data indicate (by the dose level and the magnitude of the effect) that humans are more sensitive than laboratory animals, there is no justification for reducing the 10x inter-species uncertainty factor.
>
> If the comparative data indicate (by the dose level and the magnitude of the effect) that humans and laboratory animals are equally sensitive or that humans are less sensitive than laboratory animals, consideration was given to reducing the inter-species uncertainty factor.

On **January 14, 1999,** the HIARC evaluated the oral (Coulston *et a*l., 1972; MRID No. 000112118) and the pharmacokinetic (Nolan *et al.*, 1982; 000249203) studies in humans with chlorpyrifos using the parameters developed for evaluation of the human studies. The HIARC classified these studies as *supplemental* because the results provided useful scientific information that can be used as supportive data along with the results from the animal studies, but the studies alone are not sufficient for endpoint selection or risk assessments due to technical limitations.

On **February 2, 1999,** the HIARC evaluated the doses and toxicology endpoints selected for chlorpyrifos based solely on animal toxicity studies On **February 23, 1999,** the HIARC re-convened and determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments. The HIARC's conclusions are presented in **Attachment 1**, **HIARC report dated March 4, 1999 (HED Document No. 013249)**

The reader is advised to refer to the HIARC reports listed below for details on dose and toxicology endpoint selections and FQPA assessments. The summary table presents the doses and endpoints based on animal studies that are currently used for the risk assessment of chlorpyrifos.

Date	HED Doc. No.	Report Title
February 2, 1998	012471	***CHLROPYRIFOS - FQPA REQUIREMENT*** - Report of the Hazard Identification Assessment Review Committee.
December 7, 1998	013004	***CHLROPYRIFOS - RE-EVALUATION*** - Report of the Hazard Identification Assessment Review Committee.)
March 4, 199	013249	***CHLROPYRIFOS - HAZARD IDENTIFICATION BASED ON ANIMAL STUDIES*** - Report of the Hazard Identification Assessment Review Committee.

ATTACHMENT 1

CHLROPYRIFOS - HAZARD IDENTIFICATION BASED ON ANIMAL STUDIES - Report of the Hazard Identification Assessment Review Committee.

HED DOC. NO. 013249

DATE: March 4, 1999

MEMORANDUM

SUBJECT: CHLORPYRIFOS - Hazard Identification Based on Animal Studies - Report of the Hazard Identification Assessment Review Committee.

FROM: Deborah Smegal, Toxicologist and Risk Assessor
Re-Registration Branch 3
Health Effects Division (7509C)

THROUGH: Mike Ioannou, Co-Chairman
And
Jess Rowland, Co-Chairman
And
Pauline Wagner, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Steve Knizner, Branch Senior Scientist
Re-Registration Branch 3
Health Effects Division (7509C)

PC Code: 059101

The Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met on February 2, 1999 and re-assessed the toxicology database to select toxicology endpoints based on animal studies for dietary and non-dietary exposure risk assessments. On February 23, 1999, the Committee re-convened to determine the appropriate uncertainty factors (UFs) and Margins of Exposures (MOEs), respectively for dietary and non-dietary risk assessments. The Committee's decisions are attached.

Committee Members in Attendance: Dave Anderson, Bill Burnam, Virginia Dobozy, Pam Hurley, Mike Ioannou, Tina Levine, Sue Makris, Nicole Paquette, Kathleen Raffaelle, Jess Rowland, P.V. Shah, and Pauline Wagner.

Other HED staff present at the meeting were Deborah Smegal, Re-Registration Branch 3, and

William Sette and Brenda Tarplee, Science Analysis Branch.

Data Presentation: _____
and Deborah Smegal, MPH
Report Preparation Toxicologist

Report Concurrance: _____
Brenda Tarplee
Executive Secretary

1. BACKGROUND

On **January 5, 1999**, the HIARC established criteria for evaluating the scientific validity of human studies to be used in risk assessment. Based on these criteria, the principal human studies, Coulston et al. 1972 (MRID No. 00095175) and Nolan et al. 1982 (MRID No. 00249203), previously used as the basis of the endpoints for dietary as well as occupational and residential exposure risk assessments for chlorpyrifos were determined to be supplementary for risk assessment purposes. Consequently, this document establishes revised endpoints for risk assessment based on animal studies. In addition, the HIARC compared the results of the human and animal studies and determined the uncertainty factors and margins of exposures for dietary and occupational risk assessments, respectively.

This report supersedes the previous HIARC documents with respect to toxicity endpoints (based on human studies) for use in risk assessment. However, the December 7, 1998 HIARC report (*Memorandum*: J. Rowland to D. Smegal; HED Document 013004) contains the committee's recommendation on increased sensitivity issues as they relate to the FQPA safety factor, while the February 2, 1998 HIARC report (*Memorandum*: J. Rowland to B. Madden; HED Document 012471) discusses critical scientific literature also relevant to the FQPA safety factor decision. This report presents a comprehensive presentation of the dose and toxicological endpoints selected based on animal studies as well as the UF /MOE's employed for acute and chronic dietary as well as occupational/residential human risk assessments.

II. HAZARD IDENTIFICATION

A. Acute Dietary (One-Day)

Study Selected: Concentration-Time Course of Chlorpyrifos and Chlorpyrifos-Oxon in Blood. [Non-Guideline]

MRID. Nos. 44648101 (Mendrala and Brzak 1998)

Executive Summary:

This study (MRID No.: 44648101) was done to help construct and validate a physiologically-based pharmacokinetic model for chlorpyrifos (Unlabeled - 99.8% a.i., Lot # MM930503-17; Labeled - 89.4% a.i., Lot # B930-51 [INV1134]) a weak inhibitor of acetylcholinesterase activity, and its metabolites, chlorpyrifos-oxon (OXON), a strong cholinesterase inhibitor and 3,5,6-trichloropyridinol. Groups of 24 Fischer 344 male rats were given a single gavage dose of 0.5, 1, 5, 10, 50, or 100 mg/kg chlorpyrifos in corn oil. Four rats from each group were killed 10 and 20 minutes and 1, 3, 6, and 12 hours after treatment. Cholinesterase (ChE) activity was measured in the brain and plasma at each time point, as well as the plasma concentration of the test material and its OXON metabolite. In a separate portion of the study, four male rats were given a single gavage dose of labeled chlorpyrifos at a concentration of 5 or 100 mg/kg and were sacrificed three hours later. Blood was collected from the animals at sacrifice and the concentration of the test material and its metabolites 3,5,6-trichloropyridinol (TCP) and OXON determined.

Plasma ChE activity decreased in a time- and dose-dependent manner. The plasma ChE activities of rats treated with 0.5, 1, 5 or 10 mg/kg were maximally decreased 3-6 hours after treatment, with both the decrease and recovery of activity being dose-dependent. Plasma ChE activity was not significantly inhibited in the 0.5 mg/kg group. In the 1 mg/kg dose group, plasma ChE activity was significantly inhibited approximately 28% and 40% relative to controls at 3 and 6 hours post exposure, respectively. By 12 hours post-exposure, plasma ChE activity was still significantly inhibited about 15%. The decrease in activity of rats treated with 50 or 100 mg/kg began within 10 minutes of treatment. By 12 hours after treatment, both groups were approximately 11% of the control group and had not shown signs of recovery.

Brain cholinesterase activity was not affected as dramatically by test material treatment as plasma activity with only the 10, 50, and 100 mg/kg dose groups showing significant effects. The brain cholinesterase activity of rats treated with 10 mg/kg test material began to decline within three hours of treatment and was significantly decreased by six hours after treatment. The brain cholinesterase activity in the 50 or 100 mg/kg dose groups decreased significantly within one hour of treatments; and by 12 hours, it was approximately 30% and 20%, respectively, of control. In none of the affected groups did brain cholinesterase show signs of recovery.

Peak chlorpyrifos blood concentrations occurred within three hours of treatment in all but the lowest dose group. The area under the curve (AUC) was calculated as 0.4, 1.1, 5.0, and 12.5 μmole hr L^{-1} for the 5.0, 10.0, 50.0, and 100 mg/kg groups, respectively and yielded calculated blood half-lives of chlorpyrifos of 2.7,1.5, 2.1, and 7.3 hours for the 5.0, 10.0, 50.0, and 100.0 mg/kg dose groups, respectively. Regardless of dose, the highest concentration of OXON detected was 2.5 ng/g found in the blood of rats treated with 50 mg/kg test material one hour post-treatment. Following treatment with 5 or 100 mg/kg labeled test material, $\geq$98% of the activity detected in the blood was identified as TCP metabolite with the remaining attributed to the parent compound. Since OXON is an intermediate in the formation of TCP and none of the metabolite was detected, these studies support that the half-life of the OXON metabolite is short (reportedly 10 seconds) and that *in vivo* metabolism of chlorpyrifos is rapid.

This study is considered acceptable (nonguideline). It may partially fulfill guideline requirements in other areas.

Dose and Endpoint for Establishing the acute RfD: NOAEL = 0.5 mg/kg/day based on significant 28-40% plasma ChE inhibition 3-6 hours after dosing male rats with a single dose of 1 mg/kg. Although, the blood time course study did not measure red blood cell (RBC) ChE activity, it is likely that RBC ChE inhibition would have been observed 3-6 hours post exposure at 1 mg/kg based on the results of the Special Neurotoxic Esterase Study (MRID 44273901) (see below discussion).

Comments about Study and Endpoint: Although the selected study focuses on the

phamacokinetics of chlorpyrifos, the HIARC concluded that it provides valuable information and identifies a NOAEL and LOAEL of 0.5 and 1 mg/kg/day, respectively for plasma ChE activity. HIARC concludes that the NOAEL is appropriate for this exposure period of concern (i.e., after a single dose). This is the only single dose animal study that measured cholinesterase activity at the peak time of inhibition and at intervals of 3, 6, 12 and 24 hours post-exposure. The other animal studies only measured ChE activity 24 hours post-dosing.

The Special Neurotoxic Esterase (NTE) Study (MRID 44273901) provides support for the acute RfD, and observed significant plasma ChE, RBC AChE and heart AChE of 45%, 17% and 19%, respectively 24 hours after dosing female F344 rats with 5 mg/kg/day, but no effects at 1 mg/kg/day. This study demonstrates that RBC and heart AchE inhibition are correlated with plasma ChE inhibition and would be expected to be similarly inhibited approximately 15-20% at 1 mg/kg/day during the peak period of inhibition, 3-6 hours following exposure. In addition, the female data from the NTE study support the findings of the male data from the blood time course study, as there does not appear to be gender differences in the observed toxicity of chlorpyrifos.

The human data also provide support for the acute RfD based on animal data, but indicate that humans may be more sensitive than animals to plasma ChE inhibition. No effects were observed in a human study of 4 male volunteers/dose after a single exposure to the highest dose of 0.1 mg/kg/day (plasma ChE activity ranged from 12% ↑ to 32% ↓relative to baseline measurements) (Coulston et al. 1972, MRID No.00095175). However, 6 adult males exposed to a single oral dose of 0.5 mg/kg/day exhibited peak plasma ChE inhibition of 64-88%,12 to 24 hours post-exposure and peak RBC ChE inhibition of 11-52% on post-exposure day 4 (Nolan et al. 1982, MRID No. 00249203). In the latter study, there were no clinical signs of toxicity, although the plasma ChE activity did not return to pre-dose levels until 30 days post-exposure.

Uncertainty Factor(s): The HIARC concluded that an UF of 100 is appropriate and should be used, which incorporates both factors for inter-species extrapolation and intra-species variation. The Committee concluded that a 10x for inter-species is appropriate because the effect level (0.5 mg/kg/day, 64-88% plasma ChE inhibition observed in humans) was the NOAEL in the animal study. These data suggest that humans may be more sensitive to plasma ChE inhibition than animals following acute exposures. Although the human data are not rigorous enough for endpoint selection, the human study did provide insight as to when ChE inhibition is likely to occur. The human study only included 6 male test subjects/dose and was determined to have limited test power and therefore, can only be used as supplemental data.

$$\textbf{Acute RfD} = \frac{0.5 \text{ mg/kg/day}}{100} = \textbf{0.005 mg/kg/day}$$

This risk assessment is required.

B. Chronic Dietary Risk Assessment (Reference Dose)

Study Selected: 2-Year Dog Feeding Study (McCollister et al. 1971 and Kociba et al. 1985)

MRID Nos. 00064933, and 00146519

Executive Summary:

The chronic toxicity study (MRIDs 00064933, 00146519) in dogs consisted of two phases. In Phase I, chlorpyrifos (97.2-98.8% a.i) as Dowco® 179 was administered to 3 beagle dogs/sex/dose in diet at dose levels of 0, 0.01, 0.03, 0.1, 1 or 3 mg/kg/day for one year. One dog/group was sacrificed at one year, and the remaining 2 dogs/group were sacrificed after a 3 month recovery period. In Phase II, chlorpyrifos was administered to 4 beagle dogs/sex/dose at the same dose levels for a total of two years, at which time all dogs were sacrificed.

There was a significant increase in the absolute and relative liver weights in the high dose males, although no concurrent histolopathological changes were observed. The male liver/body weight ratios were 2.6 for the control group and 3.47 for the highest dose group (which is less than a 2-fold increase). It is possible that changes in liver weight are an adaptive response. No other treatment related effects were noted other than cholinesterase inhibition. There were no treatment related effects on body weight, mortality, clinical signs, clinical chemistry, food consumption, hematology, urinalysis, or gross pathology.

Plasma cholinesterase (ChE) activity in the one-year study was significantly and dose-dependently decreased in all male and female dogs except the 0.01 mg/kg/day group. Inhibition was apparent from 7 days on-ward. Plasma ChE inhibition for the 0.01, 0.03, 0.1, 1 and 3 mg/kg/day dose groups relative to controls were 16% ↑- 26% ↓, 5-42%, 34-56%, 49-77%, and 64-82%, respectively. Cholinesterase activity returned to normal levels 14 days after treatment cessation. Plasma ChE activity in the two-year study was similar to the one-year study. Plasma ChE inhibition of 6-42%, 28-54%, 41-69% and 68-85% was noted in both sexes of the 0.03, 0.1, 1 and 3 mg/kg/day groups, respectively. In the one-year study, red blood cell ChE inhibition of 27-45%, 10-47%, 2-48%, 34-75% and 24-82% was noted in both sexes of the 0.01, 0.03, 0.1,1 and 3 mg/kg/day groups, respectively. Red blood cell ChE activity in dogs of these groups returned to normal after 92 days. Similar red blood cell ChE inhibition was observed in the two-year study, where inhibition was 1-17%, 6-41%, 37-75%, 43-87% for both sexes of the 0.03, 0.1, 1 and 3 mg/kg/day dose groups, respectively. Overall statistical significance for plasma ChE inhibition was reached at 0.03 mg/kg/day for some time intervals, while statistical significance was observed for RBC ChE inhibition at 0.1 mg/kg/day for some time intervals.

Brain ChE activity was not markedly different from controls in the one-year study, although only one dog/sex/dose was evaluated. No significant brain ChE inhibition was noted in the two-year study, although mean inhibition in males relative to controls was 1.5, 6.7, 8.3, 7.2 and 20.8% for

the 0.01. 0.03, 0.1, 1 and 3 mg/kg/day groups, respectively. In females, the brain ChE activities relative to controls were +7.1, +2.8, +1.2, +5.8 and -19.4%, respectively. The brain ChE inhibition in the high dose group is considered toxicologically significant.

The NOAELs for plasma, red blood cell and brain cholinesterase inhibition are 0.01, 0.03 and 1 mg/kg/day, respectively. The LOAELs for plasma, red blood cell and brain cholinesterase inhibition are 0.03, 0.1 and 3 mg/kg/day, respectively. The LOAEL and NOAEL for systemic effects are 3 and 1 mg/kg/day, respectively based on alterations in absolute and relative liver weights, that could be an adaptive response.

The chronic toxicity study in dogs in conjunction with the addendum that contains supplemental information are acceptable-guideline and satisfy the guideline requirement (83-1b).

Dose/Endpoint for establishing the RfD: NOAEL = 0.03 mg/kg/day based on statistically significant or biologically significant decreases in plasma and red blood cell ChE activities in both sexes exposed to 0.1 mg/kg/day for 2 years. In addition, the ChE inhibition was noted at nearly all treatment periods at 0.1 mg/kg/day. Although, significant plasma ChE inhibition was also noted at 0.03 mg/kg/day, these effects were discounted because they were considered marginal and variable, and were not always statistically or biologically significant at all intervals.

Comments about Study and Endpoint: Animal data were selected because the HIARC committee concluded that the 28 day human study (Coulston et al. 1972), selected previously as the basis of the chronic RfD, is not appropriate for the evaluation of lifetime dietary exposures because steady-state may not have been achieved. However, the Coulston et al. (1972) study provides some support for the animal data. In this study no effects were noted in humans exposed to 0.03 mg/kg/day for 21 days, while 36-82% plasma ChE inhibition and clinical signs of toxicity (blurred vision, feeling of faintness and runny nose) were observed in individuals exposed to 0.1 mg/kg/day for 9 days. Exposure of the 0.1 mg/kg/day dose group was discontinued on day 9, rendering this study of insufficient duration for assessing chronic exposures.

The NOAEL of 0.03 mg/kg/day and the LOAEL 0.1 mg/kg/day are supported by a 90 day rat study that observed marginal, but significant 22% plasma ChE inhibition at 0.025 mg/kg/day (Crown et al. 1985, MRID 40436406), and two other animal studies that observed no adverse effects at 0.01 mg/kg/day but significant plasma and/or RBC ChE inhibition at 0.22 mg/kg/day (90 day dog; Barker 1989, MRID 42172801) or 0.33 mg/kg/day (2 yr rat; Crown et al. 1990, MRID 42172801). Unfortunately, the large difference between low and mid dose groups (i.e., more than an order of magnitude) for two of these studies does not permit the evaluation of effects at 0.03 mg/kg/day. In addition, these studies are supported by the developmental neurotoxicity study that observed plasma and red blood cell inhibition of 43% and 41%, respectively relative to controls in dams exposed to 0.3 mg/kg/day (the lowest dose tested) from gestation day 6 (GD 6) through gestation day 20 (approximately 2 weeks) (Hoberman 1998a,b, MRID Nos. 44556901, 44661001).

Uncertainty Factor (UF): For chronic dietary risk assessment, the HIARC determined that an UF of 100 is required to derive the chronic RfD and that the inter-species extrapolation factor can not be altered. Although no effects were noted in both animals and humans at 0.03 mg/kg/day, the duration of exposure differs significantly (2 years for dogs and 21 days for humans). These data indicate the humans could be similarly or even more sensitive than animals to ChE inhibition. Although the human study did provide insight as to when ChE inhibition occurs, it was not rigorous enough for endpoint selection. The human study only included 4 male test subjects/dose and was determined to have limited test power and therefore, can only be used as supplemental data.

$$\textbf{Chronic RfD} = \frac{0.03 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = \textbf{0.0003 mg/kg/day}$$

This risk assessment is required.

C. Occupational/Residential Exposure Risk Assessments

1. Dermal Absorption

Study selected :- None.

MRID No.: None.

Because the registrant has not submitted a study that quantifies dermal absorption of chlorpyrifos in animals, the HIARC estimated a dermal absorption factor of 3% by comparing the dermal LOAEL of 10 mg/kg/day from the 21 day rat dermal study (Calhoun and Johnson 1988, MRID No.40972801) to the oral LOAEL of 0.3 mg/kg/day in the rat developmental neurotoxicity study (Hoberman 1998a,b, MRID Nos. 44556901, 44661001). Both LOAELs are based on cholinesterase inhibition. The resulting estimated dermal absorption is 3% (oral LOAEL of 0.3 ÷ dermal LOAEL of 10 x 100 = 3%). This absorption factor is comparable to the dermal absorption estimated from human data of 1-3% (Nolan et al. 1982, MRID No. 00249203).

Dermal Absorption Factor: **3%** (extrapolated)

2. Short-Term Dermal - (1-7 days)

Study Selected: 4-Day Dermal Probe and 21-Day Dermal Toxicity Study in Rats (Calhoun and Johnson 1988)

MRID No. 40972801

Executive Summary:

In a 21-day dermal toxicity study (MRID 40972801), 5 Fischer 344 rats/sex/dose were dermally exposed to 0, 0.1, 0.5 , 1 or 5 mg/kg/day chlorpyrifos (100% a.i.) in corn oil on a 12 cm^2 area of the back of each animal once per day, 6 hours/application, 5 days/week for a total of 15 applications in 21 days. In a 4-day dermal probe study used to select the doses, 4 female Fischer 344 rats/dose were treated via dermal application at dose levels of 0, 1, 10, 100 or 500 mg/kg/day chlorpyrifos in corn oil for four consecutive days.

In the 21-day study, there were no signs of treatment-related systemic or dermal toxicity at doses up to 5 mg/kg/day, including effects on cholinesterase inhibition, body weight, food consumption, ophthalmological examination, hematology, or clinical chemistry. In the 4-day probe study, 2 of 4 females in the 1 and 10 mg/kg/day groups developed slight erythema. Dose-related plasma (45, 92 and 98%↓) and red blood cell (16, 49 and 75%↓) cholinesterase inhibition were observed in the 10, 100 and 500 mg/kg/day groups relative to controls. However, statistical analyses were not conducted. The cholinesterase activities of the 1 mg/kg/day females were slightly decreased, but within the historical control range. No other treatment-related effects were noted in the dermal probe study.

The NOAEL and LOAEL for plasma and red blood cell cholinesterase inhibition are 5 and 10 mg/kg/day, respectively, based on the results of both the 21-day and 4-day dermal probe studies.

The combination of the 4-day probe study and the 21-day dermal study are classified as ACCEPTABLE-GUIDELINE and satisfy the guideline requirement (82-2), but not guideline 870.3200, which requires 10 animals/sex/dose for dermal toxicity testing. However, these studies were determined to be useful for risk assessment.

Dose and Endpoint for Risk Assessment: NOAEL =5 mg/kg/day based on plasma and red blood cell ChE inhibition of 45 and 16%, respectively in rats dermally exposed to 10 mg/kg/day for 4 days, but no ChE inhibition in rats exposed to 5 mg/kg/day for a total of 15 applications over a 21 day period. Because the NOAEL is from an animal study, a MOE of 100 should be used in the risk assessment.

Comments about Study and Endpoint: This study is appropriate for the route (dermal) and duration (1-7 days) of exposure concern. Both studies were used in the determination of the dose for risk assessment. In a human pharmacokinetic study, 5 white adult males dermally exposed to 5 mg/kg/day for a single dose had peak plasma ChE inhibition of 27-45% on day 3 and mean RBC ChE inhibition of 8.6% on day 4 (Nolan et al. 1982). These data indicate that humans may be more sensitive to the dermal toxicity of chlorpyrifos than animals.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: 2-Year Dog Feeding Study (McCollister et al. 1971 and Kociba et al. 1985)

MRID Nos. 00064933, and 00146519

Executive Summary: See Chronic Dietary

Dose and Endpoint for Risk Assessment: NOAEL = 0.03 mg/kg/day based on statistically or biologically significant decreases in plasma and red blood cell ChE activities in both sexes exposed to 0.1 mg/kg/day for 85-93 days in the 2 year dog study. In addition, the ChE inhibition was noted at nearly all treatment periods in the 0.1 mg/kg/day dose group. Although, in some instances, statistically and/or biologically significant ChE inhibition was also noted at 0.03 mg/kg/day following exposure for 85-93 days (11%↑- 42%↓for plasma ChE activity and 5% ↑- 47% ↓ for RBC ChE activity relative to controls), these effects were discounted because of the considerable variation between the two phases of the dog study. Statistically and biologically significant plasma and RBC ChE inhibition were more consistent at 0.1 mg/kg/day, which was considered the LOAEL. Because the NOAEL is from an animal study, a MOE of 100 should be used in the risk assessment.

Comments about Study and Endpoint: The HIARC determined that the 21 day dermal toxicity study is of insufficient duration for this (7-to 90-days) risk assessment, and consequently selected a dose (NOAEL) based on ChE inhibition observed after 85-93 days of exposure in the 2-year oral toxicity study. Since an oral dose was identified, a dermal absorption rate of 3% should be used for dermal risk assessments.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: 2-Year Dog Feeding Study (McCollister et al. 1971 and Kociba et al. 1985)

MRID Nos. 00064933, and 00146519

Executive Summary: See Chronic Dietary

Dose/Endpoint for Risk Assessment: NOAEL = 0.03 mg/kg/day based on statistically significant or biologically significant decreases in plasma and red blood cell ChE activities in both sexes exposed to 0.1 mg/kg/day for 2 years. In addition, the ChE inhibition was noted at nearly all treatment periods at 0.1 mg/kg/day. Although, significant plasma ChE inhibition was also noted at 0.03 mg/kg/day, these effects were discounted because they were considered marginal and variable, and were not always statistically or biologically significant at all intervals. Because the NOAEL is from an animal study, a MOE of 100 should be used in the risk assessment.

Comments about Study and Endpoint: This study, dose and endpoint were used for establishing the chronic RfD. Since an oral dose was identified, a dermal absorption rate of 3% should be used for dermal risk assessments.

This risk assessment is required.

5. Short- and Intermediate-Term Inhalation Exposure (1 Day to Several Months)

Study Selected: Two 90-day Inhalation Toxicity - Rat (vapor exposure) (Newton 1988, Corley et al. 1996a,b)

MRID No(s). 40013901, 40166501, 40908401

Executive Summaries: In the first study (MRID Nos.40013901 & 40166501), Fischer 344 rats (10/sex/concentration) were exposed nose only to Chlorpyrifos at vapor concentrations of 0, 5.2, 10.3, or 20.6 ppb (0, 72, 143 or 287 µg/m^3, respectively) 6 hours/day, 5 days/week for 13 weeks. Cholinesterase activity was measured at study termination. The maximum dose to rats in the 20.6 ppb group was estimated to be 0.044-0.082 mg/kg/day based on average study specific body weights of 0.15 and 0.282 kg for female and male control animals, respectively and the EPA default rat ventilation rate of 0.00715 m^3/hr (average for males and females).

There were no treatment-related effects on body weight, clinical signs, urinalysis, hematology, clinical chemistry, organ weights, gross pathologic or histopathologic evaluations, or plasma, red blood cell or brain cholinesterase activities. Although female rats of all treatment groups had a slight (<4%) but significant decrease in red blood cell count, and males of all treatment groups had slightly elevated (approximately 13%) serum urea nitrogen, these observations were not considered treatment-related due to a lack of dose-response, and all values were within the historical control range.

No LOAEL was identified in this study. Therefore, the NOAEL for systemic toxicity and cholinesterase inhibition exceeds 20 ppb or 0.082 mg/kg/day.

In the second study (MRID No. 40908401), Fischer 344 rats (10/ sex/ concentration) were exposed nose only to Chlorpyrifos (95% a.i.) at vapor concentrations of 0, 5, 10, or 20.6 ppb (0, 72, 143 or 287 µg/m^3, respectively) 6 hours/day, 5 days/week for 13 weeks. These concentrations resulted in estimated maximum exposures of 0, 0.024, 0.048 and 0.097 mg/kg/day, respectively based on the EPA default ventilation rate of 0.00715 m^3/hr for rats (average of males and females), and average study specific body weights of 0.189 and 0.127 kg for male and female controls, respectively. The study author stated that the saturation or near saturation level was 20 ppb.

There were no treatment-related effects on mortality, body weight, clinical signs, ophthalmoscopy, hematology, gross pathology or histopathology. In females, food consumption was slightly depressed throughout the study in all dose groups without correlation to the dose level, although this observation was not considered of toxicological significance due to only slight decreases in corresponding body weights. There were some sporadic differences in clinical chemistry parameters, although these were not considered treatment-related due to a lack of dose-response and inconsistency between interim and terminal values. Sporadic differences in organ weights also were not considered treatment-related and appeared to be attributed to the increase mean body weights.

Significant plasma cholinesterase (ChE) inhibition was observed in the high dose males (23%) and females (25%) at the terminal sacrifice. Significant plasma ChE inhibition was also noted in females of the 5 and 10 ppb groups (26 and 40%, respectively), although a dose-response relationship was not apparent. Interim (8 week) measurements were similar or slightly greater than controls. Red blood cell (RBC) (interim and terminal) and brain (terminal) ChE activities were not significantly inhibited at any dose level. It should be noted that the chlorpyrifos concentrations in the exposure chambers at 13 weeks were approximately 12, 16 and 24 ppb, which exceeds the 5, 10 and 20 ppb average exposure levels and this may partially explain the terminal results, while the 8 week concentrations were closer to the average levels. The plasma ChE inhibition was not considered of toxicological significance because of the minimal inhibition (23-25%) at the high dose, lack of dose-response, and an absence of inhibition in the 8 week interval.

No LOAEL was identified in this study. Therefore, the NOAEL for systemic effects and plasma cholinesterase inhibition exceeds 20 ppb or 0.097 mg/kg/day.

Dose/Endpoint for establishing the RfD: NOAEL = 0.1 mg/kg/day based on no effects on plasma or RBC ChE inhibition in two rat inhalation studies at the highest dose of 20.6 ppm (0.082-0.097 mg/kg/day) (the saturation level). The inhalation data are supported by the developmental neurotoxicity study that observed biologically significant decreases in plasma and red blood cell ChE of 43% and 41%, respectively relative to controls in rats orally exposed to 0.3 mg/kg/day (the lowest dose tested) (LOAEL) from gestation day 6 (GD 6) through gestation day 20 (approximately 2 weeks) (Hoberman 1998a,b MRID Nos. 44556901, 44661001). Because the NOAEL is from an animal study, a MOE of 100 should be used in the risk assessment.

Comments about Study and Endpoint: Animal inhalation data were selected with support from the oral data in animals. There are no human inhalation data to indicate whether humans are more sensitive than animals following inhalation exposure. The HIARC concluded that the weight of evidence indicates that an inhalation hazard from technical Chlorpyrifos is unlikely based on the following factors: 1) the low vapor pressure of Chlorpyrifos, which is 1.87×10^{-5} mmHg at 25°C (Merck Index, 11th Edition); 2) the maximum attainable vapor concentration of Chlorpyrifos is 25 ppb at 25°C; 3) the two 90 day inhalation studies (nose only) that yielded no adverse effects at concentrations up to 20 ppb or 287 $\mu g/m^3$ (0.097 mg/kg/day). However, low airborne

concentrations (< 1 $\mu g/m^3$) persist in homes at least one year following termite treatments, and at least 10 days in homes following crack and crevice treatment with chlorpyrifos, and homeowners could be exposed to air concentrations as high as 20 $\mu g/m^3$ following lawn treatment with chlorpyrifos. In addition, agricultural workers are exposed via inhalation during application to crops.

Although HIARC recognizes that human exposure to chlorpyrifos occurs through inhalation of both vapor and aerosol, a waiver for an aerosol study was previously granted in 1989. HIARC selected an inhalation NOAEL based on two vapor studies. This NOAEL is likely to overestimate the toxicity associated with aerosol inhalation exposures to an unknown degree.

This risk assessment is required.

6. Long-Term Inhalation Exposure (Several Months to Life-Time)

Study Selected: 2-Year Dog Feeding Study (McCollister et al. 1971 and Kociba et al. 1985)

MRID Nos. 00064933, and 00146519

Executive Summary: See Chronic Dietary

Dose/Endpoint for establishing the RfD: NOAEL = 0.03 mg/kg/day based on statistically significant or biologically significant decreases in plasma and red blood cell ChE activities in both sexes exposed to 0.1 mg/kg/day for 2 years. In addition, the ChE inhibition was noted at nearly all treatment periods at 0.1 mg/kg/day. Although, significant plasma ChE inhibition was also noted at 0.03 mg/kg/day, these effects were discounted because they were considered marginal and variable, and were not always statistically or biologically significant at all intervals. Because the NOAEL is from an animal study, a MOE of 100 should be used in the risk assessment.

Comments about Study and Endpoint: Oral animal data were selected because the 90 day inhalation studies are of insufficient duration to evaluate long-term exposures. Since an oral dose was identified, the inhalation absorption rate should be assumed to be equivalent to the oral absorption rate (i.e., use a default factor of 100%) for long-term inhalation risk assessments.

Although HIARC recognizes that human exposure to chlorpyrifos occurs through inhalation of both vapor and aerosol, a waiver for an aerosol study was previously granted in 1989. HIARC selected an inhalation NOAEL based on two vapor studies. This NOAEL is likely to overestimate the toxicity associated with aerosol inhalation exposures to an unknown degree.

This risk assessment is required.

D. Margins of Exposure for Occupational/Residential Exposures:

A MOE of 100 should be used for all of the occupational risk assessment scenarios because these endpoints were based on NOAELs from animal studies. The Committee concluded that an MOE of 100 is appropriate because the effect level in the single dose dermal study in humans (5.0 mg/kg) is the same as the NOAEL in the 21-day dermal toxicity study in rats which was used for dermal risk assessments. The MOEs for residential exposure risk assessment scenarios will be determined during risk characterization by the FQPA Safety Factor Committee.

E. Recommendations for Aggregate Exposure Risk Assessments

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

For **Short-Term** aggregate exposure risk assessment, route specific data are available for the oral, dermal and inhalation exposures with a common endpoint (ChEI); therefore, the following method should be used:

$$MOE_{Total} \quad \frac{1}{\frac{1}{MOE_{(Oral)}} + \frac{1}{MOE_{(Dermal)}} + \frac{1}{MOE_{(Inhalation)}}}$$

For **Intermediate-Term** aggregate exposure risk assessment route specific data were available only for the inhalation exposure whereas an oral dose was selected for dermal exposure. The dermal exposure should be converted to an oral equivalent dose (using 3% dermal absorption) and compared to the oral NOAEL to calculate the MOE. Therefore, the following method should be used:

$$MOE_{Total} \quad \frac{1}{\frac{1}{MOE_{(Oral+dermal\ oral\ equivalent)}} + \frac{1}{MOE_{(Inhalation)}}}$$

For **Long-Term** aggregate exposure risk assessment, the oral, dermal exposure converted to an oral equivalent dose (using 3% dermal absorption) and the inhalation exposure converted to an oral equivalent dose (assuming inhalation absorption is 100% of oral absorption) should be combined and compared to the oral NOAEL .

III. FQPA CONSIDERATIONS

1. Neurotoxicity Data

This issue was previously addressed in the February 2, 1998 and December 7, 1998 HIARC reports (HED Document Nos. 012471 and 013004, respectively).

2. Determination of Susceptibility

This issue was previously addressed in the February 2, 1998 and December 7, 1998 HIARC Reports (HED Document Nos. 012471 and 013004, respectively).

3. Recommendation for a Developmental Neurotoxicity Study

A Developmental Neurotoxicity Study has been submitted and reviewed for chlorpyrifos. This study was discussed in the December 7, 1998 HIARC Report (HED Document No. 013004).

IV. SUMMARY OF TOXICOLOGY ENDPOINTS SELECTION

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary	NOAEL=0.5 UF = 100	plasma cholinesterase inhibition at peak time of inhibition (3-6 hours post exposure) at 1 mg/kg.	Blood Time Course Study	NR
	Revised Acute RfD =0.005 mg/kg/day			
Chronic Dietary	NOAEL= 0.03 UF= 100	Plasma and RBC cholinesterase inhibition	2 year dog study	NR
	Revised Chronic RfD =0.0003 mg/kg/day			
Short-Term (Dermal)	Dermal NOAEL =5	Plasma and RBC cholinesterase inhibition of 45 and 16%, respectively at 10 mg/kg/day.	21-day dermal rat study	100
Intermediate-Term (Dermal)	Oral NOAEL =0.03	Plasma and RBC cholinesterase inhibition at 0.1 mg/kg/day	2 year dog study	100
Long-Term (Dermal)	Oral NOAEL =0.03	Plasma and RBC cholinesterase inhibition at 0.1 mg/kg/day	2 year dog study	100
Short-,and Intermediate-Term (Inhalation)	Inhalation NOAEL= 0.1	Lack of effects in 2 rat inhalation studies at the highest dose tested.	Two 90 day rat inhalation studies	100
Long-Term (Inhalation)	Oral NOAEL= 0.03	Plasma and RBC cholinesterase inhibition at 0.1 mg/kg/day	2 year dog study	100

NR = not relevant
UF = Uncertainty Factor